

## REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks. Upon entry of this response, claims 1, 2, 6, 7, and 19 – 21 will be pending.

Claims 1, 2 and 7 are revised to comport with the examiner's recommendations. Withdrawal of the pending objection to these claims is warranted, therefore.

By virtue of two rejections under 35 USC § 103, all of the claims stand rejected on the basis of an obviousness rationale that relies on either Bett *et al.* or Schraa *et al.* According to the examiner, each of these published U.S. applications discloses “a deletion in the E1 region” of an Ad35 vector.

While recognizing that present claims recite “a deletion between [nucleotides] 367 and 2,917 or 3,375” of the E1 region, the examiner contends that these deletion boundaries “were chosen” to effect “an E1 protein-encoding region that is functionally defective,” with no appearance of “provid[ing] an advantage over similar deletions” in the prior art illustrated by Bett and Schraa (action at page 3, third and sixth paragraphs). Thus, the examiner adopts the presumption that such E1-incapacitating deletions are fungible, one to the other, and she imposes on applicants a “burden … to show a novel or unobvious difference between the claimed products and the products of the prior art” (*id.* at page 4, lines 7 – 9). In particular, she cites *Ex parte Smith* and its underlying *KSR* precedent for the proposition that, because Bett and Schraa teach an Ad35 vector that “is deficient in E1 function,”

...it is within the ordinary skill of the art to use available methodologies to isolate a variety of vectors comprising any number of deletions that [result in] E1 activation. One would have been motivated to do so in order ... to modify sequences by applying conventional methodologies.

*Id.*, lines 18 – 22.

Thus, the examiner is heard to argue that it would have obvious to try out “a variety of vectors” in this regard, with the reasonable expectation, *a priori*, that they would be essentially “indistinguishable” from one another. Under *KSR/Smith* case law, however, an application of an “obvious-to-try” rationale is improper in this context.

More specifically, the Supreme Court's *KSR* decision prompted a reconsideration of the obvious-to-try rationale, *i.e.*, positing the obviousness choosing from a finite number of identified, predictable solutions with a reasonable expectation of success. See EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Registrar*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines."

Pursuant to the Guidelines, an examiner seeking to advance an obvious-to-try rationale is obliged to articulate:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim or claims in question would have been obvious, within the meaning of Section 103.

In the present instance, Examiner Marvich has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness. This is so because, contrary to her adopted presumption, there was insufficient understanding or insight in the contemporaneous art, concerning the impact of different E1-region deletions, for the skilled artisan to have confronted "a finite number" of deletion options with "a reasonable expectation of success" in finding given deletions suitable.

This lack of understanding is evidenced by the post-filing publication of Havenga *et al.*, *J. Gen. Virol.* 87: 2135 (2006) (copy appended). The authors report on investigating a "severe vector-genome instability" problem, heretofore unexplained, that affect "E1-deleted rAd35 vectors, hampering universal use" (abstract). Based on "[s]equence analyses of several insert-deletion mutant rAd35 vectors," Havenga *et al.* sought to "map the 5' transcription start sites within human adenoviruses" with the "hypothesis[es] that pIX protein expression might be limited in E1-deleted rAd35 vectors" (page 2138, left column).

To that time, it was known only that the “pIX gene encodes a protein that, in the context of Ad5, is important for packaging of full-length adenovirus genomes” (*id.*). Through their mapping work and other experiments, however, Havenga *et al.* showed that the “instability of E1-deleted rAd35 vector [was] … caused by low pIX expression induced by removal of the pIX promoter, which was located in the E1B region of B-group viruses” (abstract).

In light of the Havenga report, it is apparent that the skilled artisan, at the time of the present invention, could have been largely ignorant of what structural aspects of the Ad35 vector, including hitherto unrecognized elements of the E1 region, could be influenced or maintained in deletion mode and *not* impact on vector performance. For instance, Bett *et al.* teach Ad35 vector characterized by a complete deletion of E1 region, between nucleotides 457 and 3402. Pursuant to Havenga, this deletion must certainly have affected vector-genome stability, in sharp contrast to the presently claimed vector, where the pIX promoter elements located within the E1B region are maintained.

On one hand, therefore, the contemporaneous art does not comport with either the examiner’s adopted presumption of fungibility or her resultant application of an obvious-to-try rationale, consistent with *KSR/Smith*. On the other hand, applicants have shown above that their claimed vector is *not* fungible with prior-art Ad35 vectors, as illustrated by those of Bett, in a manner that could not have been predicted when the presently claimed invention was made.

On ether count, therefore, the rationale for the pending obviousness rejections is shown to be faulty, warranting reconsideration and withdrawal of those rejections. Applicants would add only that Wadell *et al.*, the secondary reference, does not compensate for the demonstrated deficiencies of either primary reference. While Wadell may teach that Ad35 has high affinity to CD35+ cells, the secondary reference does not teach or suggest “infection” of CD35+ cells by Ad35 virus. That is, even in instances when virus does bind to a cell surface, the cell itself is not necessarily acquire infected by the virus as a consequence.

### CONCLUSION

In view of the foregoing, applicants submit that the present application is in condition for allowance, and they solicit an early indication to this end. Examiner Marvich is invited to contact the undersigned directly, should she feel that any issue requires further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 CFR § 1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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